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Multielectrode

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a multielectrode for recording low amplitude bioelectrical signals originating from biopotential differences, to a method of processing signals recorded by the invented multielectrode, to a system for recording and amplifying low amplitude bioelectrical signals, and to a process for manufacturing the invented multielectrode.

BACKGROUND OF THE INVENTION

In examinations recording bioelectrical signals, such as in ECG (electrocardiography), EMG (electromyography) and ENeG (electroneurography), the bioelectrical signals are detected and recorded by electrodes. One recording electrode, especially used in ENeG, comprises e.g. two large chlorinated silver plates or two half spherical metal surfaces, e.g. of silver, applied to a patient, in the vicinity of a nerve. The size and shape of the two electrically conducting surfaces of the electrode depend on the individual application and design, the distance between them is normally fixed, e.g. to 20-30 mm, and they may be enclosed in a plastic mould. Pieces of felt material soaked in saline or some other electrically conducting liquid are positioned in the recesses holding the electrode surfaces in order to establish contact between the electrode surfaces and the skin.

The electrically conducting surfaces constituting the electrode may also be mounted individually, directly on the skin in appropriate individual positions by using adhesive tape.

When recording small amplitude signals from a peripheral limb nerve, the electrodes are positioned and fixed to the skin overlying the nerve, for example by adhesive tape or a Velcro

strap attached around the electrode and the limb. The recording electrode is preferably attached to the skin with the two electrically conducting recording surfaces positioned directly above and along the nerve, minimizing the distance between the recording surfaces and the nerve.

A very high amplification is necessary in the recording system, since the amplitude of the neural signals derived from normal human limb nerves is low, between 100 and 5 microvolt. By superimposing repeated responses or by using an averaging procedure, an improvement of the signal-to-noise ratio of successively recorded nerve responses can be achieved, such that the limit for discrimination of reliable responses is around 1 microVolt.

However, there are several drawbacks with these electrodes. Due to the low amplitude of the nerve signals, the accuracy of the recording is easily disturbed. The recording procedure may have to be repeated when other simultaneously recorded biopotentials interfere due to e.g. sweating and movements of the patient, or when concurrent 50 Hz-disturbances occur. Since an averaging procedure is utilized, the intermittent electrical stimulation used to induce the neural activity can be prolonged, thereby causing further discomfort to the patient.

Another available technique uses near nerve recording by needle macroelectrodes. A needle macroelectrode is a needle electrode with a relatively large recording area at the tip, which is inserted percutaneously (through the skin) and brought close to or in outer contact with the nerve. A reference electrode is positioned subcutaneously nearby. Since the needle tip is located close to the activated nerve fibres in near nerve recording, the signal-to-noise-ratio is improved. In combination with averaging procedures, discrimination of signals with an amplitude of only 0.5 - 0.2 microVolt is possible.

In microneurography, which is another recording technique, a solid tungsten microelectrode or a concentric electrode with an outer diameter of only 200 micrometers is inserted percutaneously and positioned intraneurally. The very small surface of the active recording electrode is brought in intimate contact with nerve fibres within an individual nerve fascicle, while the reference electrode surface is positioned nearby, thereby permitting the recording of an electroneurogram of electrically induced nerve responses derived from the entire nerve fibre spectrum, i.e. from both thick and thin myelinated fibres and from thin, unmyelinated fibres, having diameters between 20 - 1 micrometers and conduction velocities between 70 - 1 m/sec. This is the only technique in man that also allows recording from single myelinated and unmyelinated nerve fibres in response to various natural stimuli applied within the innervation area of the impaled fascicle.

However, these procedures using needle electrodes are technically very demanding, time consuming and manually difficult to execute. They are, therefore, unsuitable as clinically routine diagnostic tools.

Related art is also described e.g. in US 5,976,094.

An object of this invention is to limit or eliminate some of the described problems when recording low amplitude bioelectric signals and to provide an improved non-invasive recording electrode and a novel procedure to process the recorded signals, whereby in particular the signal-to-noise ratio of the signals is improved compared to prior techniques, making the invention suitable for clinical examinations of patients.

SUMMARY

The above object is achieved by the multielectrode, by the recording method, by the recording system and by the

manufacturing process according to the attached claims, which are hereby incorporated in their entirety.

The claims are directed to a multielectrode comprising a carrier provided with separate electrode surfaces for recording biopotential differences, the multielectrode adapted to be connected to processing means. The electrode surfaces include one or more active electrode surfaces and two or more reference electrode surfaces, thereby providing two or more recording pairs for recording biopotential differences at a detection site.

The processing means may comprise summation means for calculating the sum of the biopotential differences recorded by the recording pairs.

The active electrode surfaces may be centrally positioned on the surface area of the carrier and the reference electrode surfaces may be symmetrically positioned between the active electrode surfaces and the edge delimiting the surface area of the carrier.

The carrier may consist of two or more separate subcarriers, of which each subcarrier is provided with at least one separate electrode surface, the total number of electrode surface being at least three.

The active electrode surfaces may all have a substantially similar size and shape and the reference electrode surfaces may also have a substantially similar size and shape. The size and/or shape of the reference electrode surfaces may be substantially similar to or substantially different from the size and/or shape of the active electrode surfaces.

The surface of the carrier may be provided with elevated parts onto which electrode surfaces are attached, or with recesses

into which electrode surfaces are fitted, and the electrode surfaces may extend on the sides of the elevated parts or of the recesses of the carrier surface.

The recesses in the carrier may be delimited by vertical edges elevated from the surface of the carrier, thereby preventing short-circuiting between adjacent electrode surfaces.

Electrically conducting means may be attached to at least some of the electrode surfaces.

The carrier and/or the electrode surfaces may be provided with an adhesive for attaching the multielectrode to the detection site.

The carrier with the electrode surfaces may be formed by one or more thin layer/s/ of an insulating material provided with a pattern of electrode surfaces.

The carrier may be provided with three or more needles, of which each needle tip constitutes at least part of an electrode surface.

The claims are also directed to a method of processing signals indicating biopotential differences at a detection site, the signals recorded by the multielectrode, the method comprising a summation of the signals recorded at the detection site by at least two recording pairs. Said signals are derived from generators of biopotential differences.

An inversion of at least one of the signals may be performed prior to the summation, and a delay from the starting point of the induced response may be performed before inversion of at least one of the signals prior to the summation. At least part of one or more signals may be muted prior to the summation.

The claims are also directed to a process of manufacturing said multielectrode, at least part of the process being manual, or at least part of the process being performed by mechanical manufacturing means. The steps may comprise the manufacturing of thin layers of an insulating material, providing some of the layers with patterns of electrode surfaces and fastening and/or folding the layers together.

The claims also relates to a system for recording signals indicating biopotential differences at a detection site, the system comprising at least one multielectrode and processing means connected to said multielectrodes, the processing means comprising summation means. The processing means may further comprise inversion means, delay means and muting means.

Other features and further advantages of the invention will be apparent from the following description and the described non-limiting embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be described in more detail and with reference to the drawings, of which:

Figure 1 illustrates a top view of a presently used macroelectrode,

Figure 2 illustrates an arrangement for recording electrically evoked neural activity,

Figure 3 is a top view of a first embodiment of the invented multielectrode,

Figure 4 is a top view of a second embodiment of the invented multielectrode,

Figure 5 is a top view of a fourth embodiment of the invented multielectrode, and

Figure 6 is a block diagram illustrating one method of processing bioelectric signals recorded by the invented multielectrode.

DESCRIPTION OF THE INVENTION

One object of the invention is to improve the recording of low amplitude bioelectric signals originating from generators of biopotential differences, i.e. from nerve fibers or motor units. This is accomplished by the invented electrode, comprising a plurality of separate recording surfaces, by the invented processing method, by the invented system and by the invented manufacturing process.

Figure 1 illustrates one prior art macroelectrode 1, provided with two electrode surfaces 2a and 2b of an electrically conducting material, preferably a metallic material. The size of the prior art macroelectrode is approximately 1 cm x 2.5 cm x 5 cm, and the size of each of the two electrode surfaces is approximately 6 mm x 20 mm. The macroelectrode is intended to be fixed to the skin overlying a nerve with the electrode surfaces facing the skin.

Figure 2 schematically illustrates an arrangement for recording neural activity in a large number of nerve fibers located in a peripheral nerve at the wrist of a patient. In this arrangement, the bioelectric neural activity is evoked by repetitive electrical shocks applied to the patient at a stimulation site 3 located on one of the patient's fingers. However, bioelectrical activity may alternatively be evoked by magnetical, physical or natural stimulation, such as e.g. by skin stimulation and, in other arrangements, by voluntary muscle contractions, light flashes or sounds. A bioelectrical signal, i.e. a biopotential difference between two spots on the skin of the patient, caused

by the evoked neural activity, is detected by a recording electrode attached to the patient at a detection site 4 located on the wrist of said patient. The arrangement is further provided with appropriate electrical grounding means, which is not illustrated in this figure. The signals recorded by the electrode are processed electronically in order to obtain an optimal signal to be displayed, e.g. on an oscilloscope.

When recording bioelectrical signals in an animal, the detection site may be on the skin of the animal, or alternatively in a paraffin filled pool limited by skin flaps where the electrode surfaces are submerged to contact a nerve or some other biopotential generator in the animal, e.g. a nerve root. The electrode surfaces in the pool may be located in intimacy or close to the top or underneath the biopotential generator.

In order to improve the signal-to-noise-ratio of recorded biopotential differences at a detection site, which e.g. is located on the skin directly overlying a nerve of a patient, the novel electrode according to this invention comprises a carrier provided with a plurality of separate electrode surfaces. The electrode surfaces include one or more active electrode surfaces to be attached to the skin at a central part of the detection site, and two or more reference electrode surfaces to be attached to the skin at a small distance from the center of the detection site. The active electrode surfaces are preferably centrally positioned on the electrode carrier and the reference electrode surfaces are preferably positioned between the active electrode surfaces and the edge of the surface area of the carrier, the localization depending on the shape and size of the carrier. The reference electrode surfaces may be grouped, so that the groups located on the carrier symmetrically surround the active electrode surface or surfaces.

The recording of a biopotential difference, i.e. a bioelectrical signal, is achieved by pairs of electrode surfaces, one active

(negative) and one reference (positive) electrode surface, constituting one recording pair between which the biopotential difference is detected. By means of using multiple electrode surfaces, the biopotential difference occurring at a detection site can be detected by several recording pairs at this site, with the active electrode surface/s/ participating in more than one recording pair. Processing means, including a summation unit, connected to the multielectrode adds the recorded values of the biopotiential differences detected by each recording pair, thereby achieving an improved recording of the bioelectrical signal, i.e. regarding the signal-to-noise-ratio.

The number of active electrode surfaces provided on a multielectrode is one or more and typically between one and three. The number of reference electrode surfaces is two or more and typically between four and twenty.

The electrode surfaces of one multielectrode may have different shapes and sizes. However, if the electrode surfaces have similar shape and size, their electrical impedance is similar, which may be advantageous. According to one embodiment of the invention, all of the active electrode surfaces of one multielectrode have similar shape and size and all of the reference electrode surfaces have similar shape and size, while the size and shape of the reference electrode surfaces is different from the shape and size of the active electrode surfaces, or, alternatively, only the shape is different while the size of all of the electrode surfaces is similar.

Figures 3-5 show top views of exemplary embodiments of the invented multielectrode, provided with a multitude of separate electrode surfaces. The biopotential difference at a detection site is detected and measured by several recording pairs, each recording pair consisting of one of the active electrode surfaces and one of the reference electrode surfaces of the

multielectrode. The recorded values are processed and summed, achieving an improved recording of a bioelectrical signal.

Figure 3 illustrates a first embodiment of the invented multielectrode 5, having a rectangular electrode carrier 8, on which rectangular electrode surfaces are attached. The electrode, according to this exemplary embodiment, is provided with one group 6 of two active electrode surfaces, and with two groups, 7a and 7b, each with three reference electrode surfaces, the two groups positioned on either side of the group of active electrode surfaces 6. The multielectrode is intended to be applied to a patient with the active electrode surfaces located directly overlying the detection site, e.g. in a nerve of a patient. If the rectangular electrode carrier is positioned along the stretch of the nerve, the stretch of an individual, rectangular, electrode surface is perpendicular to the longitudinal stretch of the nerve.

Figure 4 illustrates a second embodiment of the invented multielectrode 5, having a more quadratic configuration of the electrode carrier 8, onto which separate electrode surfaces are attached. The multielectrode according to this second, exemplary, embodiment is provided with one group, 6, of three substantially quadratic active electrode surfaces and with two groups, 7a, 7b, each with five rectangular reference electrodes. In this embodiment, the three groups of electrode surfaces are located in parallel on the carrier, the group of active electrode surfaces located in between the two groups of reference electrode surfaces and intended to be located directly above the stretch of the nerve.

According to a third, not illustrated, embodiment of the invented multielectrode, the configuration of the multielectrode carrier 8 comprises two or more separate subcarriers, intended to be individually applied to the detection site 4 of a patient. Each subcarrier is provided with one or more separate electrode

surfaces, of which the active electrode surfaces preferably are positioned on the same subcarrier. The total number of electrode surfaces must be three or more.

Figure 5 illustrates a fourth, exemplary embodiment of the invented multielectrode 5, having a circular electrode carrier 8, on the elevations of which separate electrode surfaces are attached. The multielectrode is provided with only one, centrally located, active electrode surface 6 and four groups, 7a, 7b, 7c, 7d, of reference electrode surfaces, each with three reference electrodes, these four groups surrounding the active electrode surface and positioned with approximately 90 degrees angular distance from each other. The carrier surface of this embodiment may have a circular, semicircular, semiellipsoid, partly rectangular or partly square extension. According to an alternative embodiment, the electrode surfaces are attached into recesses in this type of electrode carrier.

A multielectrode according to figure 5 is mainly intended for recording of signals in a detection site from which signals are spread uniformly, which occurs e.g. when obtaining precordial leads of ECG-recordings or in surface EMG-recording.

The size of the carrier of the invented multielectrode may vary considerably depending on the application of the multielectrode, but a rectangular carrier, according to the embodiment illustrated in figure 3, may have an approximate length of e.g. 5 cm, a width of e.g. 2.5 - 3.5 cm and a thickness of e.g. 1 - 1.5 cm. The electrode surfaces may be attached in the bottom of recesses in the carrier, the recess having a depth of e.g. 10 mm, a length of e.g. 20 mm and a width of e.g. 2-4 mm. The electrode surfaces may extend on the sides of the recess. Alternatively, the electrode surfaces may be attached, e.g. glued, on elevated parts of the surface of the carrier, the elevated parts having a height of approximately up to 10 - 15 mm

and a width of e.g. 1.5 mm. The electrode surfaces may extend on the sides of the elevated parts.

Part of an electrode surface may be unexposed due to insulating material covering part of the surface.

The individual size of an exposed or unexposed electrode surface depends on the application, but is typically between 40 - 150 mm^2. However, the electrode surface may be as small as a few mm^2 and larger than 200 mm^2.

By extending the electrode surfaces on the side of recesses or on elevated parts of a carrier, a larger electrode surface area is possible, whereby e.g. a lower impedance can be achieved.

The distance between adjacent electrode surfaces, i.e. the interelectrode distance, may vary according to the application, the size of the carrier and the size and shape of the electrode surfaces, but may typically be between 1 mm and 2 mm. However, by varying the interelectrode distance, various degrees of packing and/or grouping of active and of reference electrode surfaces can be achieved.

The distance between the electrode surfaces of one recording pair depends e.g. on the size of the electrode carrier and the location of the reference electrodes in relation to the active electrodes. It is normally between 12 mm and 20 mm, but may be shorter or longer. The variations in the distances between the electrode surfaces constituting the recording electrode pairs on one multielectrode is, however, preferably less than 5 mm.

Electrically conducting material, such as e.g. a gel or a moist absorbing fabric or felt soaked in e.g. saline, may be attached to the electrode surfaces in order to establish the contact between the electrode surface and the skin. The attachment may be achieved e.g. by pressing the electrically conducting

material into recesses or wrapping it around elevations and holding it in place by plastic pieces or by appropriately adopted o-rings.

The carrier and/or the electrode surfaces may be provided with an adhesive in order to secure the attachment of the electrode to the skin of the patient.

The electrode surfaces are electrically insulated from each other by plastic, mould or by air, and are individually connected to shielded conductors within a cable, which feeds the obtained signals from a recording pair individually into the processing means.

Recesses in the carrier may be delimited by thin, vertical edges elevated from the horizontal surface of the carrier, thereby preventing short-circuiting between neighboring electrode surfaces placed in said recesses.

According to another embodiment of the invented multielectrode, the multielectrode is manufactured in a thin version, as a stick-on electrode, adapted to be fastened to the skin of a patient with adhesive tape. The multielectrode may be formed by one or more thin layer/s/ of mould of semi-elastic plastic, which are provided with various patterns of electrode surfaces, the individual layers separated from each other by insulating layers. By cutting and/or folding of one or more layer/s/ and gluing them together, flat multielectrodes of different design may be achieved.

According to another embodiment of the invented multielectrode, the carrier is provided with three or more needles of which the needle tip constitutes an electrode surface, or part of an electrode surface. Such a multielectrode is adapted to penetrate the skin of a patient.

The signals from the recording pairs of the multielectrode are fed to processing means, connected to the multielectrode, and summed in summation means, thereby achieving the desired improved signal-to-noise-ratio. The recordings from different recording pairs can have different polarity. However, a common polarity is preferably defined in the processing means and an inversion of some of the recordings may be performed before the summation.

If the bioelectrical signal is evoked by repetitive electrical stimulation and recorded by a large number of recording pairs, the electrical stimulation signal, i.e. the stimulus artefact, which preceeds the nerve response, may cause a saturation of the summation unit, thereby distorting the recording. This can be avoided by providing delay means, whereby a cancelling of the stimulus artefact can be accomplished by inverting some recorded signals with a delay after the artefact, thus inverting only the neural response and not the corresponding artefact. Alternatively, the parallel amplifiers connected to the summation unit may be muted for the duration of the electrical stimulus, thereby providing muting means. Also, according to this invention, some of the nerve responses must be inverted before summation.

Figure 6 is a block diagram illustrating one method of processing signals recorded by one embodiment of the invented multielectrode 5, which is only provided with one active electrode surface 6 and two reference electrode surfaces 7a, 7b. Biopotential differences in the skin overlying a nerve of a patient are detected and measured by two recording pairs 9a, 9b, of which 9a consists of electrode surfaces 6 and 7a and 9b consists of electrode surfaces 6 and 7b. The recording pairs are connected to amplifying and filtering means 10a, 10b, from which the output signals are fed to inverting and delaying means 11a, 11b. The output signals from the inverting and delaying means are connected to summation means 12. The summed signals are,

subsequently, displayed by display means 13, which may comprise e.g. a personal computer or an oscilloscope.

The multielectrode may be manufactured by suitable e.g. mechanical manufacturing means, and part of the manufacturing process may be manual. A substantially flat multielectrode may be manufactured by fastening together, e.g. by glue, thin layer/s/ of very thin plastic or other insulating material, of which some of the layer/s/ are provided with various patterns of electrode surfaces.

Thus, by the described multielectrode comprising a plurality of separate recording surfaces, by the parallel processing of the signals recorded by the multielectrode, by the system comprising the multielectrode and processing means and by the manufacturing of these items, an improved recording of low amplitude bioelectric signals, originating from biopotential differences, can be accomplished.

The invention is not restricted to the described embodiments in the figures, but may be varied freely within the scope of the attached claims.

CLAIMS

1. Multielectrode (5) comprising a carrier (8) provided with separate electrode surfaces for recording biopotential differences, the multielectrode adapted to be connected to processing means, **characterized in** that said electrode surfaces include one or more active electrode surfaces (6) and two or more reference electrode surfaces (7a, 7b), thereby providing two or more recording pairs (9a, 9b) for recording biopotential differences at a detection site (4).

2. Multielectrode according to claim 1, **characterized in** that the multielectrode is adapted to be connected to processing means comprises summation means (12) for calculating the sum of the biopotential differences recorded by the recording pairs (9a, 9b) at a detection site.

3. Multielectrode according to claim 1 or 2, **characterized in** that the active electrode surfaces (6) are centrally positioned on the surface area of the carrier (8).

4. Multielectrode according to claim 3, **characterized in** that the reference electrode surfaces (7a, 7b) are symmetrically positioned between the active electrode surfaces and the edge delimiting the surface area of the carrier.

5. Multielectrode according to claim 1 or 2, **characterized in** that the carrier (8) consists of two or more separate subcarriers, each subcarrier provided with at least one separate electrode surface, the total number of electrode surfaces being at least three.

6. Multielectrode according to any of the previous claims, **characterized in** that the active electrode surfaces (6) all have a substantially similar size and shape.

7. Multielectrode according to any of the previous claims, **characterized in** that the reference electrode surfaces (7a, 7b) all have a substantially similar size and shape.

8. Multielectrode according to any of the previous claims, **characterized in** that the size and/or shape of the reference electrode surfaces (7a, 7b) is substantially different from the size and/or shape of the active electrode surfaces (6).

9. Multielectrode according to any of the claims 1 - 7, **characterized in** that electrode surfaces all have a substantially similar size and shape.

10. Multielectrode according to any of the previous claims, **characterized in** that the surface of the carrier (8) is provided with elevated parts onto which electrode surfaces are attached.

11. Multielectrode according to claim 10, **characterized in** that at least one of the electrode surfaces extend on the sides of the elevated parts of the carrier surface.

12. Multielectrode according to any of the claims 1 - 9, **characterized in** that the carrier (8) is provided with recesses into which electrode surfaces are fitted.

13. Multielectrode according to claim 12, **characterized in** that at least one of the electrode surfaces extend on the sides of the recesses in the carrier surface.

14. Multielectrode according to claim 12 or 13, **characterized in** that the recesses in the carrier (8) are delimited by vertical edges elevated from the surface of the carrier, thereby preventing short-circuiting between adjacent electrode surfaces.

15. Multielectrode according to any of the previous claims, **characterized in** that electrically conducting means is attached to at least some of the electrode surfaces.

16. Multielectrode according to any of the previous claims, **characterized in** that the carrier (8) and/or the electrode surfaces are provided with an adhesive for attaching the multielectrode (5) to the detection site (4).

17. Multielectrode according to any of the claims 1 - 9, **characterized in** that the carrier (8) with the electrode surfaces is formed by one or more thin layer/s/ of an insulating material provided with a pattern of electrode surfaces.

18. Multielectrode according to any of the claims 1 - 9, **characterized in** that the carrier (8) is provided with three or more needles, of which each needle tip constitutes at least part of an electrode surface.

19. A method of processing signals indicating biopotential differences at a detection site (4), said signals recorded by a multielectrode (5) according to any of the claims 1-18, **characterized by** a summation of the signals recorded at said detection site by at least two recording pairs (9a, 9b) of the multielectrode (5).

20. A method according to claim 19, **characterized by** an inversion of at least one of the signals prior to the summation.

21. A method according to any of claims 19 or 20, **characterized by** a delay from the starting point of the induced response before inversion of at least one of the signals prior to the summation.

22. A method according to any of claims 19 - 21, **characterized by** muting of at least part of one or more signals prior to the summation.

23. A process of manufacturing a multielectrode (5) according to any of the claims 1 - 18, **characterized in** that at least part of the process is manual.

24. A process of manufacturing a multielectrode (5) according to any of claims 1 - 18, **characterized in** that at least part of the process is performed by mechanical manufacturing means.

25. A process according to claims 23 or 24 of manufacturing a multielectrode (5), **characterized by** the following steps: Manufacturing thin layers of an insulating material; Providing some of the layers with patterns of electrode surfaces; Fastening and/or folding the layer/s/ together.

26. A system for recording signals indicating biopotential differences at a detection site (4), **characterized in** that the system comprises at least one multielectrode (5) according to any of the claims 1 - 18 and processing means connected to said multielectrodes, said processing means comprising summation means (12).

27. A system for recording signals, according to claim 26, **characterized in** that the processing means further comprises inversion means.

28. A system for recording signals, according to claims 26 or 27, **characterized in** that the processing means comprises delay means.

29.A system for recording signals, according to any of the claims 26 - 28, **characterized in** that the processing means comprises muting means.

ABSTRACT

The invention comprises a multielectrode (5) comprising a carrier (8) provided with separate electrode surfaces for recording biopotential differences at a detection site. The multielectrode is adapted to be connected to processing means. The electrode surfaces include one or more active electrode surfaces (6) and two or more reference electrode surfaces (7a, 7b), thereby providing two or more recording pairs for recording biopotential differences at the detection site. The processing means comprises summation means for calculating the sum of the biopotential differences recorded at the detection site.

(Fig 3)

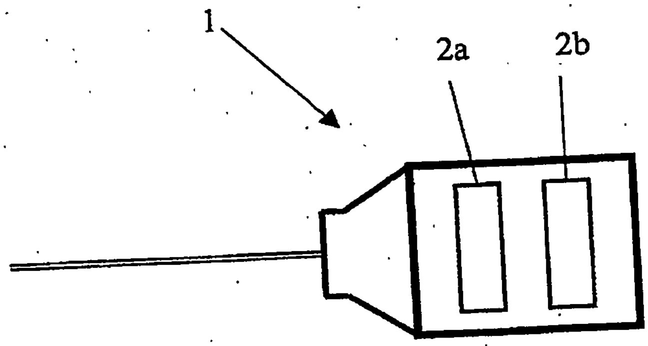

Fig 1

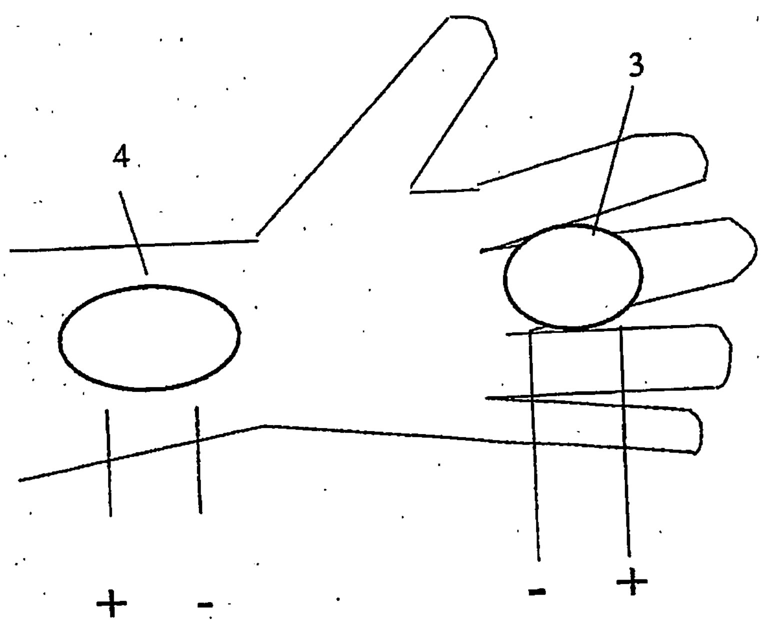

Fig 2

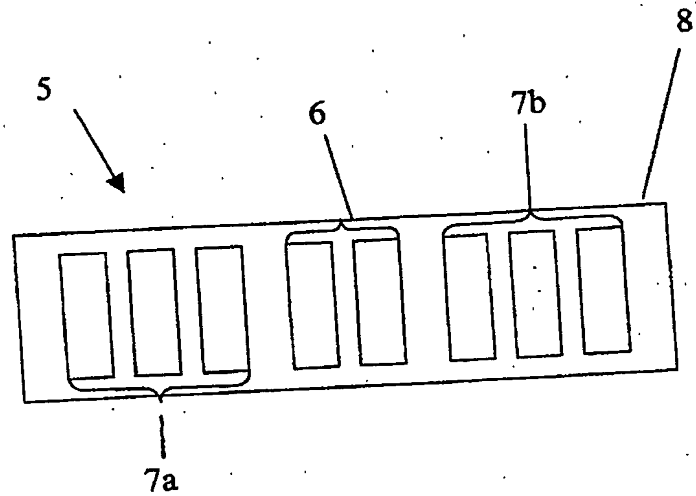

Fig 3

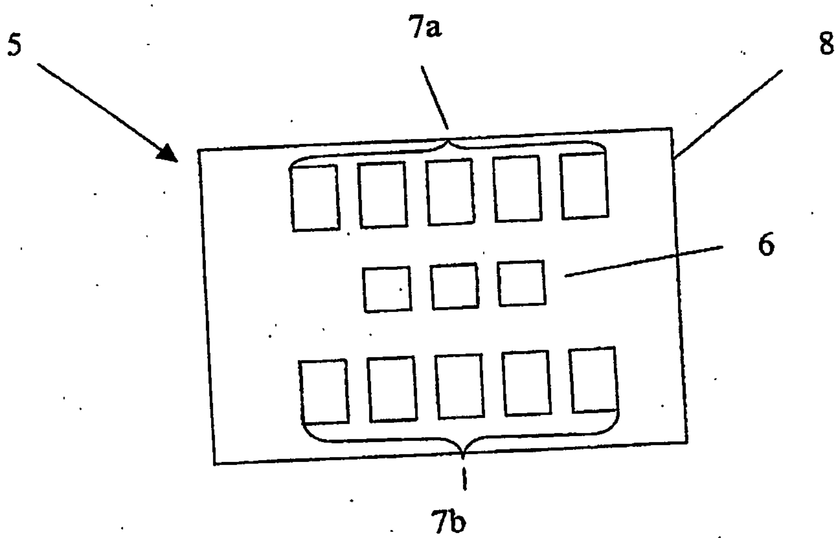

Fig 4

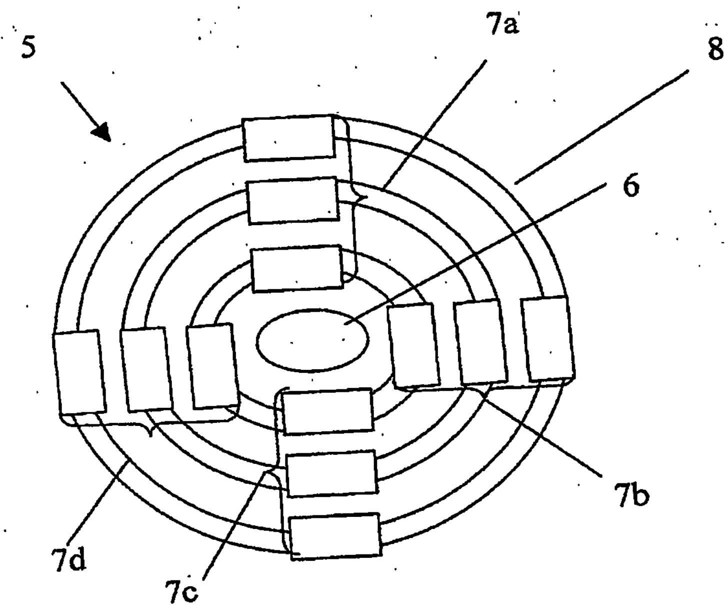

Fig 5

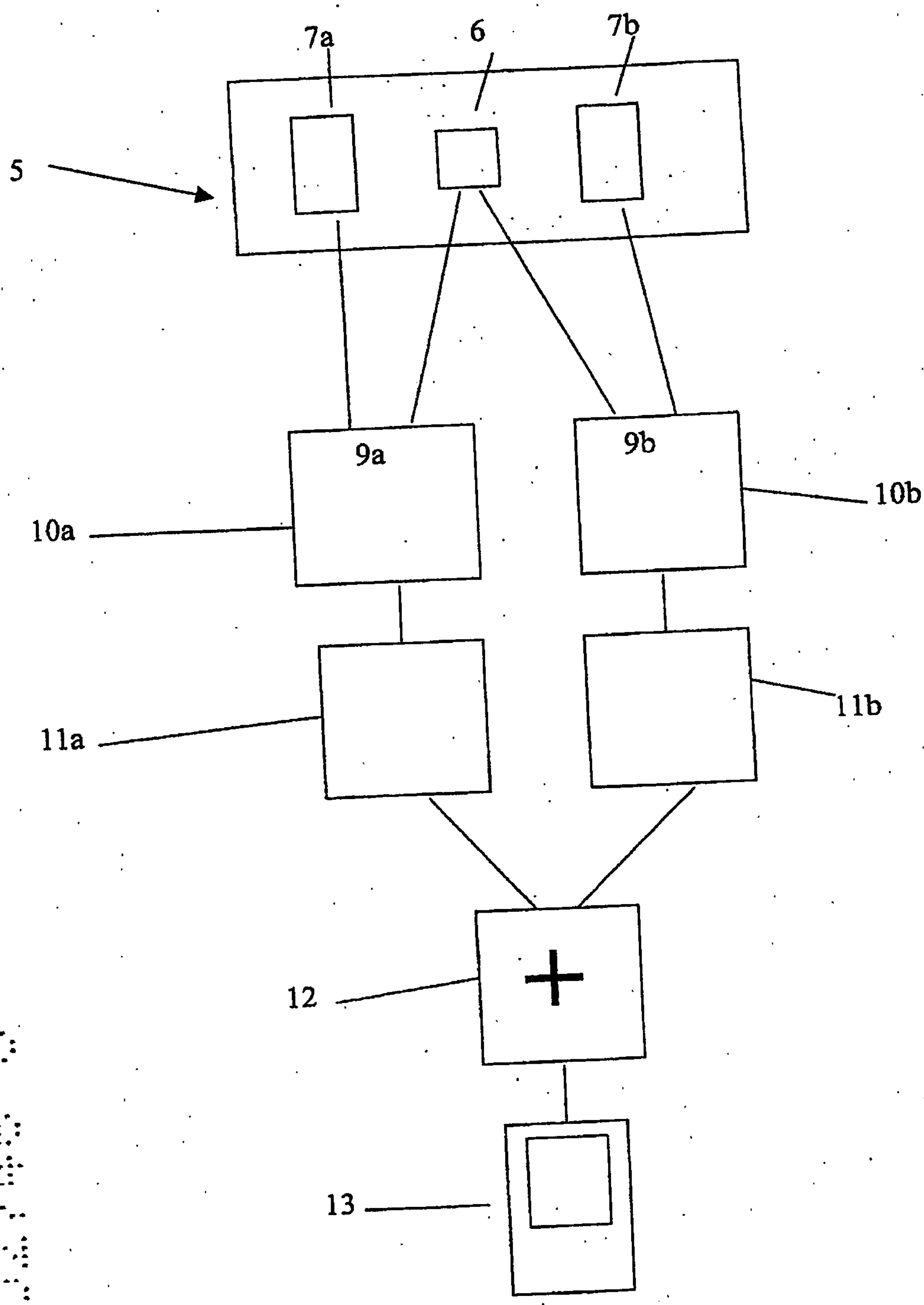

Fig 6